of page 3 of the Office Action dated October 6, 2005 that any *E. coli* adenylate kinase "may not correspond" to the intended amino acid and that "some prior art references may disclose the amino acid numbering of a sequence beginning at the first amino acid of a single sequence, while other references may not include the signal sequence" are indicative of the Examiner's lack of evidence to support the contention that the claims are indefinite. Withdrawal of the Section 112, second paragraph, rejection of claims 108-109, 111, 115-116 and 120-135 is requested.

The Section 112, first paragraph, rejection of claims 117-119, 125-127 and 133-135 stated in paragraph 11 on page 4 of the Office Action dated October 6, 2005, is traversed. The applicants noted on page 11 of the Amendment of August 5, 2005, that specific support for the claim amendments may be found in the art and, for example, in European Application No. 92110808.0, which is referred to in the present specification. The applicants should not be required to re-teach what was known in the art. Withdrawal of the Section 112, first paragraph, rejection stated in paragraph 11 of the Office Action dated October 6, 2005, is requested.

Similarly, the applicants submit that the Amendment of August 5, 2005, is not believed to have introduced new matter and withdrawal of the Section 112, first paragraph rejection of claims 108-109, 115-116 and 120-125 stated in paragraph 12 of the Office Action dated October 6, 2005, should be withdrawn.

The Section 112, first paragraph, rejection of claims 107-135 stated in paragraph 13 of the Office Action dated October 6, 2005, is traversed. The Examiner's assertion that the genus of luciferase polypeptides and corresponding encoding nucleic acids of the claims of the instant application do not share a common structural feature is not

believed to be correct. Specifically, one of ordinary skill in the art will appreciate from, for example, the references of record, that luciferases share a common related structure as well as function. Accordingly, withdrawal of the Section 112, first paragraph, rejection of claims 107-135 stated in paragraph 13 of the Office Action dated October 6, 2005, is requested.

The Section 112, first paragraph, rejection of claims 107-135 stated in paragraph 14 of the Office Action dated October 6, 2005, is traversed. The Examiner's basis for rejecting the claims in paragraph 14 of the Office Action of October 6, 2005, appears to be based, at least in part, on the assertion that "it is not routine to alter every amino acid within a given sequence with any of the 19 other common amino acids in order to isolate those that have the desired activity/utility." See, page 8 of the Office Action dated October 6, 2005. The applicants note that one of ordinary skill in the art would not be required to alter every amino acid to make and use the presently claimed invention. More likely, one of ordinary skill in the art would make an amino acid sequence which has the luciferase activity based on the present specification with some alternations, perhaps according to their own further requirements. The present specification then provides guidance for one of ordinary skill in the art to determine whether such further proteins are within the presently claimed invention. One of ordinary skill in the art would not alter every amino acid within a given sequence to make every conceivable protein within and outside of the presently claimed invention. Such a teaching should not be required. The claims are submitted to be supported by an enabling disclosure and withdrawal of the Section 112, first paragraph, rejection of claims 107-135 is requested.

The Section 103 rejection of claims 107-108, 110-115 and 120-124 over Backman, Squirrell (WO 96/02665), Squirrell (WO 96/22376) and Gilles, as stated in paragraph 15 of the Office Action dated October 6, 2005, is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

As previously-described in the record, the presently claimed invention requires a combination of the use of the desired protein which is stable under given conditions and undesired protein which is unstable under the same conditions wherein the undesired protein is one which hinders the use of the desired protein that has activities essential for the survival of the host cell or for a viable production process using a host cell. Exemplified desired proteins include luciferase and undesired proteins are exemplified in the present application as by adenylate kinase. The Examiner has combined the noted references through an inappropriate use of hindsight.

The results of Backman relate to the use of thermostable enzymes wherein a thermostable form of an enzyme is used in a recombinant production method followed by application of extreme heat to denature all but the desired peptide. See, column 2, line 53 through column 3, line 17 of Backman. Backman does not teach luciferase production.

More importantly, the process of Backman does not require production or engineering of proteins or polypeptides as required by the presently claimed invention. That is, a luciferase produced according to method of Backman would only require production of thermostable forms of luciferase in a mesophilic host cell, culturing the mesophilic host cell to produce the thermostable luciferase and purify the thermostable

luciferase by at least heating to a temperature sufficient to inactivate the unwanted contaminants but not sufficient to inactivate the thermostable luciferase. See, column 2, lines 21-37 of Backman.

Backman does not describe or suggest the simultaneous production of a desired polypeptide in a mutant form which has increased tolerance to a particular reaction condition, such as pH or temperature, as well as a mutant form or an undesired protein which has a decreased tolerance to the reaction condition as compared to a wild-type form of the undesired protein and wherein the undesired protein hinders the use of the polypeptide product and has an activity that is essential for survival of a host cell or for a viable production process using a host cell. Backman therefore provides a process wherein the identification or use of a mutant of the undesired peptide of the presently claimed invention would not be required. The combination of Gilles and/or either of the Squirrell references cited by the Examiner, with Backman therefore would not be logical to one of ordinary skill in the art wishing to produce luciferase in the process of Backman.

Reconsideration and withdrawal of the Section 103 rejection of claims 107-108, 110-115 and 120-124 stated in paragraph 15 of the Office Action dated October 6, 2005, are requested.

The Section 103 rejection of claims 117-119 and 125-127 stated in paragraph 16 of the Office Action dated October 6, 2005, is traversed. Reconsideration and withdrawal of the rejection are requested as the Examiner's secondary references (i.e., Novagen and Kiel) fails to cure the deficiencies noted above with regard to Backman and Squirrell and Gilles.

The applicants further submit that the cited references would not have motivated one of ordinary skill to have made the presently claimed invention. To a certain extent, the applicants believe the cited references would not have been considered by one of ordinary skill in the art to be analogous art. Specifically, Backman is believed to relate to the field of enzymes obtainable from thermophilic organisms, such as those required for use in techniques such as PCR. Squirrell however is concerned with different types of enzymes, with different functions from different sources, such that the enzymes of Squirrell possess different properties. Luciferases are thermosensitive enzymes obtainable from sources such as fireflies and used in signaling systems. Gilles is believed to relate to yet another field and is a scientific paper relating to a structure-activity relationship of yet another different enzyme (i.e., adenylate kinase). The Novagen and Kiel references discuss techniques used in biotechnology generally however there are not believed to be anything in the cited art which would have motivated one of ordinary skill in the art to combine the references in the manner asserted by the Examiner to have made the presently claimed invention.

Reconsideration and withdrawal of the Section 103 rejection of claims 117-119 and 125-127 stated in paragraph 16 of the Office Action dated October 6, 2005, are requested.

The Section 103 rejection of claims 107, 109-114, 116 and 128-132 over Backman in view of Squirrell (1), Kajiyama (Biochemistry 32:13795-13799) and Gilles stated in paragraph 17 of the Office Action dated October 6, 2005, is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above as well as the following distinguishing comments.

Beyond the above noted deficiencies of Backman, the applicants further note that Backman does not describe or suggestion a simultaneous production of a desired polypeptide in a mutant form which has increased tolerance to a particular reaction condition, such as pH or temperature, as well as a mutant form of an undesired protein which has decreased tolerance to the reaction condition as compared to a wild-type form of the undesired protein and wherein the undesired protein hinders the use of the polypeptide production and has an activity that is essential for survival of a host cell or for a viable production process using the host cell. Backman therefore provides a process wherein the identification or use of a mutant of the undesired polypeptide of the presently claimed invention will not be required. The combination of Gilles, which describes the identification of adenylate kinase, with Backman therefore would not be logical to one of ordinary skill in the art wishing to produce luciferase in the process of Backman.

Kajiyama teaches a mutant thermostable luciferase and also that "one of the most important goals of protein engineering is to produce mutant enzymes which have greater thermostability than the parent protein". See, page 13795, left column, second full paragraph of Kajiyama. One of ordinary skill in the art reading Kajiyama and Backman would, at best, be motivated to produce luciferases which could be sufficiently thermostable to be expressed in a mesophilic host cell of Backman. The preferred temperatures of purification according to Backman is 80°C to 95°C. See, column 3, lines 14 and 15 of Backman. The thermostable mutant luciferase of Kajiyama was tested at 50°C and found to have a half-life which was roughly 8-10 times longer than that of the wild-type luciferase. See, page 13796, right column on the first full

paragraph, and Figure 3 of Kajiyama. Even if one of ordinary skill in the art reading Kajiyama and Backman would have been motivated, at least, to produce further luciferase mutants with even greater thermostability, such is not the subject of the presently claimed invention. The further teaching of Squirrell (1), is not believed to cure the deficiencies of the combination of Backman, Kajiyama and Gilles.

Withdrawal of the Section 103 rejection of claims 107, 109-114, 116 and 128-132 stated in paragraph 17 of the Office Action of October 6, 2005, is requested.

The Section 103 rejection of claims 117-119 and 133-135 over Backman, Squirrell (1), Kajiyama, Gilles, Novagen and Kiel, stated in paragraph 18 of the Office Action dated October 6, 2005, is traversed. Reconsideration and withdrawal of the rejection are requested as the further cited references of Novagen and Kiel fail to cure the above-noted deficiencies of the other recited references.

Withdrawal of the Section 103 rejection of claims 117-119 and 133-135 stated in paragraph 18 of the Office Action dated October 6, 2005, is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned if anything further is required in this regard.

Respectfully submitted,

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